REMARKS

Claims 1-13 are pending in the Application. 1-3 and 5-9 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Kim *et al*, U.S. Patent No. 5,648,225 ("Kim") in view of Loken, *et al*, U.S. Patent No. 5,047,321 ("Loken"). For the reasons described and deemed "persuasive" during the interview, as set forth and presented below, reconsideration and withdrawal of the rejection is respectfully solicited, and prompt allowance of all pending claims is expected.

Discussions during the interview were directed to Claim 1, and its recited elements comprising the method claimed. This claim, as previously amended, reads presently as follows:

Claim 1:

A method for discrimination and counting erythroblasts comprising the steps of:

(i) staining leukocytes in a hematologic sample by adding a fluorescent leukocyte binding antibody to the hematologic sample to bind the leuckocytes;

(ii) raising the permeability only of cell membranes of erythroblasts in the hematologic sample to a nucleotide fluorescent dye which does not permeate a cell membrane when the permeability is not raised, the nucleotide fluorescent dye having a fluorescent spectrum that is distinguishable from that of a fluorescent labeling compound of the fluorescent labeled antibody in step (i);

(iii) staining nuclei of the erythroblasts in the hematologic sample with the

nucleotide fluorescent dye;

(iv) analyzing the hematologic sample using flow cytometry to detect the nucleotide fluorescent signal of the stained erythroblasts and the fluorescent signal of the labeled antibody bound to the leukocytes; and

(v) plotting the nucleotide fluorescent signal and the fluorescent labeled antibody signal in two coordinate axes to obtain a two-dimensional distribution chart discriminating between erythroblasts and leukocytes in the hematologic sample based on the difference in the two-dimensional distribution chart and counting the erythroblasts.

According to the Examiner, the citation of Kim, in view of Loken, present a *prima facie* case of obviousness supporting rejection of this claim, and the other dependent claims 2-3 and 5-9.

The interview began with a discussion of the recited steps of Claim 1 in view of the disclosure of Kim. Kim discloses a multipurpose reagent for analysis of a whole blood sample. (Abstract). Per Kim, one embodiment of the reagent allows "for the quantitative analysis of nucleated red cells on automated hematology analyzers" (Column 8, lines 32-34) features an added "nuclear stain, e.g., ethidium homodimer." (Column 8, lines 35-38). Kim then discloses that "This one-reagent process of the present invention allows one to rapidly distinguish the different leukocyte populations from nucleated erythrocytes and is particularly useful for certain veterinary applications" (Column 8, lines 51-54). Kim also discloses another separate embodiment, allowing "for the quantitative analysis of lymphocyte subpopulations" (Column 8,

lines 66-67) and instructs "mixing fluorochrome-conjugated monoclonal antibodies... with whole blood samples before adding the multipurpose reagent system." (Column 9, lines 1-5).

To understand the basis for the rejection in the cited patents and the Examiner's arguments, Applicant requested the Examiner explain where in Kim steps (i)-(iii) of Claim 1 were disclosed, taught or suggested. In response, the Examiner regarded Claim 1, step (i), as corresponding to the embodiment disclosed in Kim wherein the nuclear stain is added to the reagent system to allow for quantitative analysis of nucleated red blood cells. The Examiner regarded step (ii) as corresponding to the operation of the reagent system disclosed by Kim. As to element (iii), the Examiner felt this element had been disclosed by Kim in the embodiment wherein the labeled antibody is added to a blood sample to allow for quantitative analysis of lymphocyte subpopulations.

The discussion continued with reference to steps (iv)-(v) of Claim 1. The Examiner contended that the step of comparing a fluorescent signal of the nucleic stain against the fluorescent signal of the labeled antibody was disclosed by Kim in Figure 3(b). Applicant disagreed, pointing out that this figure plotted a red fluorescence (representing the nucleic stain embodiment of Kim) against Side Scatter Light emissions, and not against a fluorescent labeled antibody signal (indeed, Figure 3(b) is disclosed in Kim as relating solely to the nucleic stain embodiment and is not referenced in connection with any use of a fluorescent labeled antibody--see Kim, Column 8, lines 55-65). After reviewing this figure, both the Examiner and her Supervisor agreed that it apparently did not meet the elements of Claim 1 as recited.

Applicant also pointed out to the Examiner that, in a prior interview with the Examiner and her Supervisor Long Le, in October, 2002, Applicant demonstrated that the embodiments of Kim, one adding nuclear stain, the other adding the labeled antibody, were

separate embodiments of the reagent system. Referencing this prior interview, Applicant commented that no disclosure in Kim taught, disclosed or suggested any amalgamation or combination of these embodiments or to adjust either embodiment to achieve a result of the claimed process, i.e., discrimination and counting of erythroblasts. Indeed, Applicant pointed out that Kim describes only the "one-reagent" process, with nuclear stain, as allowing for distinguishing nucleated erythrocytes for unspecified "quantitation" on an automated analyzer. As the labeled antibody, as disclosed, is used for "quantitative analysis of lymphocyte subpopulation" and is neither added to the reagent (it is mixed "before adding the multipurpose reagent system"--see Column 9, lines 4-5) nor administered in a process using the nuclear stain, Applicant commented that the disclosure of Kim in fact teaches away from the claimed method.

Acknowledging the lack of teaching, disclosure and suggestion in Kim, the Examiner also referenced Loken as demonstrating plotting of nucleotide fluorescence against fluorescent labeled antibody signals. The Examiner conceded, however, that the type of nucleotide fluorescent dyes called for in Loken are disclosed as a type which "label[s] the DNA and RNA in each cell", e.g., Thiazole-Orange and LDS 751, and conceded these would be ineffective to plot erythrocytes (and, Applicant would therefore add, erythroblasts) as these cells lack both RNA and DNA. Applicant therefore contended that charts plotting nucleotide fluorescence against labeled antibody fluorescence (e.g. CD45), such as in Loken figure 3(b), are inapplicable to Applicant's claim and, indeed, indicate that proposed combination of Loken with Kim would lack any appreciable expectation of results, and may be inoperative to meet the method and objectives recited in Claim 1. Unsurprisingly, the disclosure of Loken is apparently not concerned with quantifying erythroblasts, and states, with respect to groupings of cells that only dimly express levels of fluorescence to the RNA/DNA stains and CD45, "...from this figure

it is obvious that there is no clear separation between the population of cells colored light blue (i.e., up to 3% erythroid--according to Table I) and the other painted populations." Loken, Column 10, lines 26-29).

To reject claims to a method, the references relied upon by the Examiner must account for all the manipulative steps claimed. *In re Magat*, 112 USPQ 317, 319 (CCPA 1957). Here, neither Kim nor Loken, taken together or separately, disclose a method for the discrimination and counting of erythroblasts, let alone the recited steps of Applicant's Claim 1. As such, the rejection does not account for all claimed limitations, and, falls far short of providing the requisite motivation to deviate from Kim, the primary reference according to the Examiner, to arrive at the claimed invention.

In a *prima facie* case of obviousness the citations, not interpretations of what is in the art generally, must "suggest the desirability of the combination" that is claimed. See MPEP 2143.01 at 2100-110, 111 and MPEP 2145 (j) 3 at 2100-127. This MPEP section further requires that "Obviousness can only be established by combining or modifying the teaching of the prior art to produce the claimed invention where there is *some teaching, suggestion or motivation* to do so..." (Emphasis added). No teaching, suggestion or motivation in Kim or Loken supports any modification of the disclosures therein to arrive at what the Applicants have claimed.

Lastly, the Examiner's prior assertions in each Office Action issued, which in summary, place the motivation, suggestion or disclosure in one of skill in the art, and general objectives to improve hematological analysis cannot provide this required suggestion, teaching, motivation, disclosure or method steps which Kim and Loken clearly lack. The requisite suggestion and motivation cannot be supplied by mere statements as to the Examiner's belief that the requisite motivation is within "the level of skill in the art." *Al-Site Corp. v. VSI Int'l Inc.*, 50

USPQ2d 1161 (Fed. Cir. 1999). The Examiner must adduce support for this statement or it is insufficient for a *prima facie* case under §103. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988)) Picking and choosing aspects of the recited method which may appear in the prior art does not suffice to render the claimed method, as a whole, obvious.

In sum, the Examiner has not adduced factual support demonstrating the requisite motivation for the combination of references advanced against Applicants' claims. In addition. the citations fail to account for all the Applicants' claim limitations and lack any disclosure motivating their combination. The Examiner has not met her burden of demonstrating a *prima facie* case of obviousness, therefore, the rejection should be withdrawn. Moreover, as all remaining claims under rejection (either based on the combination of Kim and Loken alone, or further in view of "Inami") also depend from Claim 1, which is clearly allowable, the rejection should be withdrawn as to all pending claims subject thereto.

As Applicant stated in the interview, prosecution of this application in view of either Kim or Loken , either alone or in combination with other patents, (such as "Inami"), has been ongoing for years. Claim 1, as it reads presently, has been pending in the application since October, 2001. Since that time, Applicant has addressed no less than three separate rejections based on Kim. Furthermore, in traversing the latest iteration of rejection, the Examiner's Supervisor pronounced Applicant's arguments, in his own words, "persuasive" during the interview. It so follows that Claim 1, and all remaining claims depending thereon, all of which have been fully searched and considered by the Examiner, have survived all contentions of anticipation and obviousness raised. Given this, fairness dictates, and Applicant expects nothing less than, the withdrawal of the instant rejection, and allowance of all claims.

In view of the foregoing, favorable action on the merits, and allowance of all claims, respectfully is solicited.

Respectfully submitted,

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